REMARKS

The Official Action dated January 24, 2005 has been carefully considered. It is believed that the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

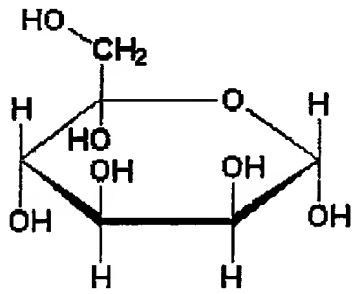
We confirm that the written description and enablement rejections have been withdrawn and that claims 23, 25-26, 31-39, 57, 59-60, and 70, 64-73 are allowed.

35 USC § 102

The Examiner has rejected claims 74 and 78 to 80 under 35 U.S.C. 102(b) as anticipated by Friesen (CA 1,201,063). Specifically, the Examiner has stated that Friesen teaches a Rh immune globulin stabilized by the addition of mannitol, and that page 18 of the instant specification defines non-ionic surface active agents as including mannitol. Applicant respectfully disagrees with the Examiner.

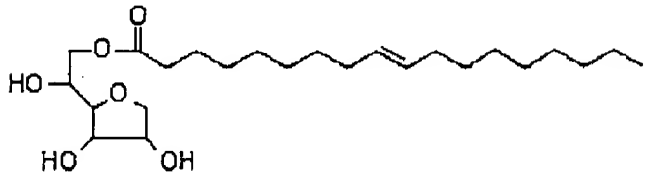
Applicant respectfully submits that the Examiner has misinterpreted page 18 of the instant specification. Page 18 teaches that non-ionic surface active agents are composed of a sugar alcohol (polyhydroxyl) that is attached via an ester group to a fatty acid. Applicant submits that mannitol is well known to be an alditol – that is, a molecule made by reducing the carbonyl group of a sugar to a hydroxyl (See Fig. 1 below). For a surface active agent to be synthesized, the free hydroxyl groups of the dehydration products of sorbitol or mannitol (i.e. sorbitan and mannitan) must be further reacted with fatty acids (typically higher fatty acids such as oleic, stearic, palmitic, miristic, caproic acid) to create esters (such as sorbitan oleate, See Fig 2 below).

Fig. 1 Mannitol



D-Mannitol

Fig. 2 Sorbitan Oleate



In conclusion, mannitol is not a surface active agent, and Friesen accordingly does not teach an aqueous immune globulin preparation for parenteral administration comprising a highly pure polyclonal anti-RhoD immune globulin and at least one non-ionic surface active agent. Applicant respectfully requests that the Examiner withdraws the rejection of claims 74 and 78-80 under 35 U.S.C. 102(b) as anticipated by Friesen.

The Examiner has rejected Claims 74-76 and 80 under 35 U.S.C. 102(b) as anticipated by DeBurgh Bradley et al (CA 1,303,533) (hereinafter referred to as "Bradley"). Specifically, the Examiner has stated that Bradley teaches an aqueous immune globulin formulation for parenteral administration comprising a monoclonal or polyclonal anti-RhD immune globulin and at least one non-ionic surface active agent. Applicant respectfully disagrees with the Examiner.

Applicant submits that Bradley teaches an Immune globulin preparation for in vitro testing that includes a non-ionic surface active agent. Bradley does not teach a composition that is suitable for parenteral administration.

Bradley (page 13, lines 16-25) teaches passive immunization with monoclonal anti-RhoD antibody. However, that section teaches a sterile solution of the antibody formulated in "any physiologically acceptable aqueous media, for example isotonic phosphate buffered saline or serum". Tween 80 or any other surfactant is not described as physiologically acceptable. De Burgh Bradley does not provide any suggestion that Tween or any other surfactant can also be advantageous in immune globulin preparations for injection into humans.

In an alternate aspect of the invention, Bradley teaches an aqueous solution of anti Rh(D) monoclonal antibody for the typing of red blood cells. In this context, there are two descriptions of solutions containing anti-RhD antibodies and the non-ionic surface acting agent Tween (80 or 20). Both solutions are diluents used in immunoassays as follows:

a) Page 14, lines 11 to 19 describe antibody dilutions required for certain in vitro assays involving RhD antibodies. Page 14, lines 20 to 28 teaches suitable diluents for blending antibodies for these assays, including physiological saline or phosphate buffered saline, "advantageously containing bovine serum albumin and a surfactant or suspending agent such as Tween 80™ or methyl cellulose."

b) Page 29 lines 9 to 17 (example 2) – Teaches Tween 20 as a diluent for a solution containing blended RhD antibodies together with KH2PO4, Na2HPO4 and NaN3. This solution is used in an indirect antiglobulin (IAG) assay.

In the above-described solutions, Tween is included in a diluent used to dilute the antibody into a larger volume prior to use in an in vitro assay. This is contrary to the

preparation of medicines for injection into humans, where one wishes to inject the smallest volume possible.

It is very clear that the preparations of anti-RhD taught by Bradley on page 14 on lines 20 to 28 are unsuitable for and not intended for parenteral administration to humans. In example a) described above, the use of bovine serum albumin is completely incompatible with parenteral administration to humans due to immunogenicity and other safety issues; only human serum albumin would be appropriate The RhD antigen is present only in humans and rhesus monkeys, and is not found in bovines, and thus Bradley cannot be contemplating a parenteral formulation for bovines.

Methyl cellulose is not approved as a non-medicinal ingredient for any parenteral formulation in Canada (where patent is issued) (http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nmi_list10_e.htm#2 - limiting dose applies to internal routes, defined as buccal, dental, ophthalmic, rectal, oral, inhalation, irrigation, nasal, vaginal, and sublingual routes, but not including im/iv), for any parenteral use in the United Kingdom (location of the assignees and where research was done) (http://www.medicinescomplete.com/mc/excipients/current/noframes/EXC0141.htm) or approved by the FDA for intravenous use.

Methyl cellulose has been demonstrated to have a significant toxicity profile when administered parenterally to animals, causing anaemia and leucopenia in dogs and leucopenia in rabbits. Intravenous injection of a 1% solution in rabbits induced subintimal deposits of methylcellulose at arterial walls followed by extensive calcification, ossification, cartilage formation and lipid deposition. Accordingly, there are no trials of methylcellulose's parenteral toxicity in man. (http://www.inchem.org/documents/jecfa/jecmono/v05je54.htm)

Methyl cellulose solutions are also prone to microbial spoilage, making it an innappropriate choice for formulations intended for storage and shipping, as opposed to diluent preparations constituted on the spot for in vitro assays. This problem is

worsened by methycellulose's known incompatibilities with common antimicrobial preservatives used in pharmaceutical preparations, such as phenol, chlorocresol, methyl, propyl and butylparabens.
(http://www.medicinescomplete.com/mc/excipients/current/noframes/EXC0141.htm)

In example b) described above, the solution that contains Tween 20 described on page 29, could be lethal if injected into a patient as it includes, KH2PO4, Na2HPO4 and NaN3 – NaN3 is a highly toxic compound. Additionally, potassium injected intravenously, at high doses, may stop the heart. As such, parenteral formulations cannot contain potassium.

The use of surface active agents in in vitro diagnostic testing is well known to those skilled in the art. Surfactants such as Tween have long been used to reduce non-specific binding in in vitro antibody assays such as those described by Bradley; other roles for surface acting agents include faster wetting, faster reaction times, reduced reagent precipitation, faster solubilization, dispersion of reagents, emulsification of reagents, increased reproducibility of results, and reduction of air bubbles in samples (http://www.che.utexas.edu/georgiou/Protocols/ProtocolFiles/ELISA.htm, http://www.researchd.com/rdioem/surfkt.htm).

From the above analysis, it is clear that in Bradley, two distinct types of solutions containing anti-RhoD antibodies are taught: a concentrated formulation for human parenteral administration consisting of antibodies in "physiologically acceptable aqueous media, for example isotonic phosphate buffered saline or serum" but not including surface active agents, and diluted preparations of anti-RhoD antibodies for use in in vitro diagnostic assays, potentially containing surface active agents such as Tween 80 or 20, but also containing elements that are toxic to humans, such as bovine serum albumin or NaN3, or are inappropriate for use in parenteral formulations of antibodies for administration to humans, such as methyl cellulose. There is no teaching in Bradley that the addition of polyoxyethylene sorbitan monooleate (Tween 80) is advantageous in an immune globulin pharmaceutical preparation. The only teaching is

that Tween 80 or 20 may be a component in antibody dilution solutions used in in vitro assays to determine the Rh-typing of red blood cells; those skilled in the art will appreciate the many reasons a surface acting agent may be present in an antibody diluent for in vitro assays. There is no connection between antibody diluents used in in vitro assays and immune globulin formulations for parenteral use in humans. Moreover, to a person skilled in the art, de Burgh Bradley does not teach a parenteral formulation of immune globulin with a non-ionic surfact active agent.

Applicant respectfully requests that the Examiner withdraws the rejection of claims 74-76 and 80 under 35 USC § 102(b) as anticipated by DeBurgh Bradley et al.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to our Deposit Account No. 50-0462.

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, she is kindly requested to contact the undersigned at her convenience.

Respectfully submitted,

4/22/2005

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